REMARKS

Claims 1-3, 6-25, 27, and 37-39 are pending in the application. Claim 16 has been amended and claims 40-41 have been added. No new matter has been added by virtue of the amendments, support being found throughout the specification and from the pending claims (see e.g., p. 16, lines 16-30).

35 U.S.C. § 103(a) Rejections

Judd, Berg, and Foo

Claims 1-3, 6, 7, 9, 12-22, 24, and 37-39 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,910,112 to Judd et al (hereinafter "Judd"), U.S. Patent No. 5,128,121 to Berg et al. (hereinafter "Berg"), and U.S. Patent Application No. 2002/0087067 to Foo (hereinafter "Foo"). Applicants respectfully traverse.

As set forth by Applicants, ^{23}Na MRI is capable of detecting altered sodium levels and, thus, may be capable of detecting myocardial infarction which results in impaired sodium-potassium pump functions. However, clinical applications of ^{23}Na MRI are limited by the low in vivo concentrations and MR sensitivity of endogenous sodium, which translates to coarse spatial resolution and low sensitivity. As further set forth, the problem of low spatial resolution is further compromised by the high sodium content of ventricular blood, with results in an intense signal for ventricular blood present in the ventricular cavities. Thus, there tends to be minimal signal intensity differences between the ventricular cavities and infracted cardiac tissue, which makes it difficult to detect infracted myocardium tissue.

Applicants provide a method for evaluating myocardial tissue using ^{23}Na or ^{39}K magnetic resonance imaging (MRI). Applicants treat the myocardial tissue with an iron oxide contrast agent so as to reduce the intensity of the ^{23}Na or ^{39}K MRI signal for ventricular cavity blood and viable well-perfused tissue. Thereafter, the heart is imaged with ^{23}Na or ^{39}K magnetic resonance to detect infracted myocardial tissue. By treating the myocardial tissue with an iron oxide

contrast agent, maximum contrast between the ventricular cavity and infarcted myocardial tissue is provided.

As set out by Judd, ^{23}Na image intensity is approximately 100% higher in non-viable compared to viable regions following reperfused myocardial infarction, as demonstrated in an animal model (col. 1, lines 54-57). This specific signal increase of 100% is reflected only in a particular time-frame post-reperfusion. However, according to Judd, MR sensitivities for ^{23}Na signals, as well as ^{39}K are very small (col. 1, lines 61 – col. 2, line 3). Thus, Judd provides strategies for maximizing ^{23}Na and ^{39}K signal acquisition to make ^{23}Na imaging of the human heart practical (col. 2, lines 54-64). In particular, Judd increases voxel size, lengthens imaging time taking, employs fast imaging pulse sequences, uses GRE imaging, and varies the selection of receiver bandwidth(see e.g. col. 6, lines 10-11, 19-21, 57-59, and 66-67) to increase the overall MR signals for ^{23}Na and ^{39}K to a detectable level.

As admitted by the Office, Judd does not teach the use of an iron oxide contrast agent so as to attenuate the ^{23}Na or ^{39}K MRI signal for ventricular cavity blood and viable well-perfused tissue. In fact, Applicants respectfully submit that Judd does not at all teach or suggest the use of contrast agents.

Applicants' further note that even with the administration of iron oxide, Judd's technique still would not have resulted in Applicants' invention. Judd only briefly discusses the presence of the two transverse relaxation components (the fast T2f and slow T2s components) for sodium and potassium. Judd does not teach or suggest that there is an interaction of superparamagnetic iron oxide contrast agent within the molecular environment, what that interaction is, or its effect, if any, on T2f and T2s. Further, Judd's technique relates to the use of fast pulse sequences (such as Gradient Echo [GRE] sequences) with long echo times (TE $\geq$ 2.5 ms). This would lead to significant reductions of the fast T2f component of sodium (depending on tissue/blood T2f relaxation values), thereby significantly decreasing the total image signal, and probably minimizing interaction of such a T2-weighted effect with the cardiac tissue. Applicants, on the

other hand, use an ultra-fast pulse sequence acquisition technique based on spiral data sampling with twisted projections with ultrashort echo times (down to 0.37 ms) that allows Applicant to capture/measure the fast T2f component of the sodium nucleus.

Applicants respectfully submit that Berg does not remedy these deficiencies in Judd.

Unlike Judd, which describes ^{23}Na and ^{39}K techniques without any type of contrast agent, Berg describes the use of a mixture of positive and negative contrast agents for MRI on the ^{1}H nucleus. Further, Berg is focused on imaging of the liver. Applicants respectfully submit that a combination of Berg and Judd would not have provided Applicants' invention.

Both the ^{23}Na and ^{39}K nuclei (which Judd is directed to) are quadrupolar nuclei and behave differently and distinctly from the ^{1}H nucleus (which Berg is directed to). Both ^{23}Na and ^{39}K nuclei exhibit biexponential transverse and longitudinal relaxations (T1fast, T1slow, T2fast, and T2slow) in contrast with ^{1}H (single exponential relaxation both for T1 and T2). Consequently, the interaction of a contrast agent (positive or negative) will follow different dynamics and interact at the molecular environment differently for ^{1}H in comparison with ^{23}Na and ^{39}K. Neither Berg nor Judd present any results or discuss the interaction of contrast agents on the quadrupolar nucleus of ^{23}Na or ^{39}K. Both Berg and Judd fail to teach or suggest an effect of signal reduction in an image as a result of the administration of iron oxide contrast agents in connection with ^{23}Na and ^{39}K techniques.

Thus, clearly, Judd and Berg simply do not teach or suggest Applicants' invention.

Foo also does not remedy the deficiencies in Judd and Berg. Foo describes a technique for MR perfusion imaging. MR perfusion imaging is generally performed by injecting a contrast agent into the blood stream and imaging the target site. According to Foo, when a contrast agent is administered into the blood stream of a patient and the myocardial tissue is subjected to MR imaging, the ventricular blood pool will exhibit a high signal intensity with respect to adjacent

stationary tissue of the vessel structure [0010]. Thus, Foo applies a pulse sequence that includes a slice-selective inversion pulse and a notched inversion pulse, wherein the (1) slice selective inversion pulse is designed to suppress myocardial tissue and the (2) notched inversion pulse is designed to suppress blood pool about the region of interest [0016]-[0017].

In other words, Foo uses a contrast agent, which is required in MR perfusion imaging. In order to address the lack of differentiation in the signal between ventricular blood, healthy tissue, and infracted tissue, Foo uses a combination of a slice-selective inversion RF pulse and a notched inversion RF pulse.

Thus, while Foo uses an imaging technique to resolve the problem of signal differentiation, Applicants use a contrast agent.

Applicants further note that Foo's approach applies to the case of one single imaging slice or a few imaging slices. Applicants', on the other hand, reduce the signal from the entire three-dimensional heart tissue, in the entire vasculature and all blood filled ventricular cavities.

Applicants respectfully submit that there is no teaching or suggestion to modify and combine the Judd, Berg, and Foo references as proposed by the Office. Applicants further submit that, even if Judd, Berg, and Foo were combined, Applicants invention still would not be taught or suggested.

Judd is the only reference that is related to a method for ^{23}Na or ^{39}K MRI imaging. Judd is directed towards increasing the overall magnetic resonance (MR) signals for ^{23}Na and ^{39}K to detectable levels. Judd does not at all teach or suggest that the presence of ventricular blood in the ventricular cavities can cause a problem with ^{23}Na or ^{39}K MRI imaging of infracted myocardium tissues, if this problem can be solved, and if so how. Judd does not at all teach or suggest the use of contrast agents in connection with ^{23}Na or ^{39}K MRI imaging. Berg is the only reference that suggests the use of contrast agents to increase or decrease signals. However, Berg

describes the use of a mixture of positive and negative contrast agents for MRI to provide improved ^{1}H MRI. As noted herein, the interaction of a contrast agent (positive or negative) will follow different dynamics and interact at the molecular environment differently for ^{1}H in comparison with ^{23}Na and ^{39}K. Berg does not teach or suggest ^{23}Na or ^{39}K MRI imaging of infracted myocardium tissues, that the presence of ventricular blood in the ventricular cavities can cause a problem with ^{23}Na or ^{39}K MRI imaging of infracted myocardium tissues, or how and if this problem can be solved. Foo is the only reference that at all suggests the problem of lack of signal differentiation between ventricular blood, healthy tissue, and infracted tissue. However, Foo addresses this problem by using a combination of a slice-selective inversion RF pulse and a notched inversion RF pulse.

The Office acknowledges that Judd does not expressly teach the use of an iron oxide contrast agent so as to attenuate the ^{23}Na or ^{39}K MRI signal for ventricular cavity blood and viable well-perfused tissue. However, the Office points to Berg and Foo. Applicants respectfully submit that neither Berg nor Foo teach or suggest ^{23}Na or ^{39}K MRI of the heart. Further, while Foo points out the problem of lack of signal differentiation between ventricular blood, healthy tissue, and infracted tissue, Foo points out that this problem exists <u>even when a contrast agent is injected</u> and MR perfusion imaging is carried out. According to Foo, this lack of signal differentiation is solved by the use of a slice-selective inversion RF pulse and a notched inversion RF pulse. While Berg uses contrast agents - in particular, positive and negative contrast agents – Berg's use of contrast agents is in connection with ^{1}H - <u>not</u> ^{23}Na or ^{39}K MRI. Further, Berg's use of contrast agents is not in connection with lack of signal differentiation between ventricular blood, healthy tissue, and infracted tissue (Berg is directed to MRI of the liver).

In view thereof, Applicants respectfully submit that there is no teaching, suggestion, or motivation to combine Judd, Berg, and Foo as proposed by the Office. Further, even if Judd, Berg, and Foo were combined, Applicants' claimed invention still would not be taught or suggested absent impermissible hindsight reasoning.

Accordingly, claims 1 and 16 are patentable over Judd, Berg, and Foo. Claims 2-3, 6, 7, 9, 12-15, 17-22, 24, and 37-39 depend from claims 1 and 16 and, thus, also are patentable over Judd, Berg, and Foo. Reconsideration and withdrawal of the rejection is respectfully requested.

Judd, Berg, Foo, and Weissleder

Claims 8, 10-11, 23, 25, and 27 are rejected under 35 U.S.C. §103(a) over Judd, Berg, Foo, and U.S. Patent No. 5,492,814 to Weissleder (hereinafter "Weissleder").

As set forth above, Judd, Berg, and Foo fail to teach Applicants' independent claims 1 and 16.

Weissleder does not remedy these deficiencies. Weissleder describes a method for preparing monocrystalline superparamagnetic particles for MRI and for collecting data from biological tissue using magnetically active compounds, such as paramagnetic compounds, for magnetic resonance imaging (MRI). Weissleder does not at all relate to ^{23}Na or ^{39}K MRI imaging of infracted myocardial tissues. Weissleder further does not teach or suggest that that the presence of ventricular blood in the ventricular cavities can cause a problem with ^{23}Na or ^{39}K MRI imaging of infracted myocardium tissues, whether this problem can be solved, and if so how. Weissleder fails to teach or suggest a method for evaluating myocardial tissue using ^{23}Na or ^{39}K MRI wherein the myocardial tissue is treated with an iron oxide contrast agent so as to selectively attenuate the ^{23}Na or ^{39}K signal for ventricular cavity blood and well-viable perfused tissue, as recited in Applicants' claim 1.

Accordingly, claims 1 and 16 are patentable over Judd, Berg, Foo, and Weissleder. Claims 2-3, 6, 7, 9, 12-15, 17-22, 24, and 37-39 depend from claims 1 and 16 and, thus, also are patentable over Judd, Berg, Foo, and Weissleder. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,

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